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EXAMINER

FORD, ALLISON M

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1651

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/524,187	Applicant(s) ZECH ET AL.	
	Examiner ALLISON M. FORD	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-19, 23 and 27 is/are pending in the application.
- 4a) Of the above claim(s) 5-7, 15, 18 and 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4, 8-14, 16, 17, 19 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>20050209; 20070730</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Election/Restriction***

Applicant's election with traverse of Group I, drawn to a method of producing cell lines, in the reply filed on 8/28/3008 is acknowledged. The traversal is on the ground(s) that search and examination of both inventive groups would not place an undue burden on the Examiner, and that search and examination of all claims in a single application would promote streamlined examination and compact prosecution. Applicants also assert that filing multiple patent applications would not serve public interest because of the fees involved and the burden placed upon the public which would be caused by having to search through multiple patent files.

The arguments have been fully considered, but are not found persuasive. The instant application is a national stage application under 35 U.S.C. 371 and is dictated by PCT Rules 13.1 and 13.2. See M.P.E.P. §801. Neither burden, on the Examiner or on the public resulting from the need to search multiple patent files, nor filing fees associated with filing of multiple applications are considerations in a finding of lack of inventive unity; rather, according to M.P.E.P. §1850, the only consideration is whether the inventions share a special technical feature. For the reasons made of record, the methods of Inventions I and II lack unity of invention *a priori*, and thus the restriction between the inventions is still deemed proper and is therefore made FINAL.

Claims 2-19, 23 and 27 are pending in the current application, of which claims 5-7, 15, 18 and 23 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being directed to non-elected inventions and/or non-elected species of the elected invention. Claims 2-4, 8-14, 16, 17, 19 and 27 have been considered on the merits.

Priority

The instant application is a national stage entry under 35 USC 371 of PCT/AT03/00232, filed 8/11/2003, which further claims priority under 35 USC 119(a)-(d) to Austrian application A1206/2002, filed 8/9/2002. A certified copy of the foreign priority document is present in the application file.

For clarity the claims are summarized below, with limitations directed to non-elected inventions and species being omitted:

Claim 27 is the only independent claim. All claims depend directly from claim 27 unless otherwise noted. Claim 27 is directed to a method for producing cell lines comprising:

(a) cultivating a non-human blastocyst under conditions that enable further development of the blastocyst to occur in stages in which newly formed cell lines having a high degree of differentiation are produced;

(b) supplying differentiable donor cells to the blastocyst to produce cell lines; and

(c) isolating the cell lines;

wherein a cells of the internal cell mass of the blastocyst have restricted survivability in comparison to a corresponding wild type or survivability of the cells of the internal cell mass is reduced through selected cultivation conditions; and

wherein the donor cells supplied to the blastocyst have varying degrees of differentiation and are of non-embryonic origin.

Claim 13 requires that, before step (b), supplying the donor cells into the blastocyst, the donor cells are brought into contact in culture dishes with other blastocysts or internal cell masses isolated from other blastocysts, and those donor cells having a relatively high contact affinity are isolated and supplied to the blastocyst in step (b).

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Claim 14 requires that, before step (b), supplying the donor cells into the blastocyst, the donor cells are equipped with a genetic marker that ensures cells having a lower degree of differentiation are isolated and supplied into the blastocyst.

Claim 17 requires that the donor cells are supplied to a blastocyst through injection.

The following claims further define/limit the donor cells:

Claim 2 requires the donor cells to contain naturally occurring stem cells, yet of non-embryonic origin (per claim 27).

Claim 4 requires the donor cells to be obtained from umbilical cord blood.

Claim 10 requires the genome of the donor cells to contain a vector which causes a resistance to additives of culture medium.

Claim 19 requires the donor cells to be human donor cells.

The following claims further define/limit the non-human blastocyst:

Claim 3 requires the cells of the internal cell mass of the blastocyst to be prepared in a culture dish or are used to prepare a soluble matrix fraction.

Claim 8 requires the cells of the internal cell mass of the blastocyst to be tetraploid cells.

Claim 9 requires the genome of cells of the internal cell mass of the blastocyst to contain a vector that causes a lethal sensitivity to appropriate cultivation conditions in comparison to the corresponding wild type [cells].

Claim 12 depends from claim 9, and further requires the survivability of the cells of the internal cell mass of the blastocyst to be reduced in a way that is tailored to the varying degrees of differentiation of the donor cells and is chronologically well-ordered.

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Claim 11 requires the survivability of the cells of the internal cell mass of the blastocyst to be reduced by adding selected antibodies.

Claim 16 requires the blastocyst to be a pig blastocyst.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 8-14, 16, 17, 19 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 limits the donor cells to be "of non-embryonic origin"; however, because all cells are technically of 'embryonic origin' (as the embryo is technically the source of all cells in an organism), it is not clear what cells are intended for use in the claimed method. It appears Applicants are intending for the limitation "donor cells of non-embryonic origin" to exclude totipotent ES cells derived directly from the embryo, such as in US 2002/0062493 (See Specification paragraphs 0002-0011 of PGPub); however the specification does not clearly define the term "cells of embryonic origin" as limited to ES cells, and thus "cells of non-embryonic origin" cannot be interpreted as any cell *except* ES cells. Because the claims must be given their broadest reasonable interpretation and, as stated previously, because all cells are technically of 'embryonic origin' the current claims are considered to exclude *all* cells. Therefore the claims are considered indefinite because it is not clear which cells may be used in the current methods. All dependent claims inherit the deficiency of claim 27, and therefore are included in the rejection.

Claim 3 is further held as indefinite, as it is not clear how the claim is further limiting the method of parent claim 27. It appears claim 3 is directed to a method of culturing cells of the ICM of the

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blastocyst separate from the blastocyst; however, this does not correlate with the method of the parent claim, which requires the blastocyst to remain intact for injection of donor cells into the blastocyst.

Clarification is required. For purposes of applying art claim 3 is being interpreted as requiring the *entire* blastocyst (not just the cells of the ICM) to be cultured in a culture dish.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-4, 8-14, 16, 17, 19 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geiger et al (Cell, 1998), in view of Tsukamoto et al (US Patent 5,914,108) and Eggan et al (US 2002/0062493).

Geiger et al disclose a method of testing plasticity of hematopoietic stem cells (HSCs) by injecting human bone-marrow derived HSCs into murine blastocysts, and detecting if the human HSCs gave rise to any cells in the resulting embryos/offspring.

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Specifically, Geiger et al isolated human HSCs from bone marrow, using antibodies to ensure selection of true HSCs (*i.e.* having a lower degree of differentiation as compared to more mature hematopoietic cells) (See Geiger et al Pg. 1063, Experimental Procedures: Purification of Hematopoietic Stem Cells), which reads on what Applicants are calling 'employing a genetic marker to select donor cells having a lower degree of differentiation' for subsequent injection to the blastocyst (claim 14). The isolated HSCs are then injected into murine blastocysts which are provided *ex vivo* (See Geiger et al, Pg. 1063, Experimental Procedures: Blastocyst Injection), which reads on 'supplying differentiable donor cells to the blastocysts' (claims 1, step (b), claim 3 and claim 17). The HSC-injected blastocysts were then either implanted into a surrogate mother, or maintained *ex vivo* on methylcellulose cultures (See Geiger et al, Pg. 1063, Experimental Procedures: Culture of Blastocysts After HSCs Injection); such culture conditions are considered to read on what Applicants are calling 'conditions that enable further development of the blastocyst to occur in stages in which newly formed cell lines having a high degree of differentiation are produced' (claim 1, step (a)). Cells were recovered from the cultured blastocysts at varying stages, including from mature offspring, for testing (See Geiger et al, PG. 1064, Experimental Procedures: RNA Analysis); this is considered to read on what Applicants are calling isolation of cell lines (claim 1, step (c)).

The human HSCs read on the 'donor cells' of the instant invention, as they have varying degrees of differentiation, and are of non-embryonic origin, as required by claims 1, 2 and 19.

The human HSCs differ from those used in the instant claims in that they are derived from bone marrow, not cord blood; however at the time the invention was made it was known that HSCs may be obtained from multiple sources, including the bone marrow and umbilical cord blood (See, e.g. Tsukamoto et al, col. 3, line 40-48). Therefore, because bone marrow and umbilical cord blood were recognized in the art as both being sources of the same HSC it is submitted that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to alternatively utilize

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HSCs from cord blood in the method of Geiger et al, for the predictable result of obtaining identical HSCs for injection into the blastocysts. (claim 4).

The mouse blastocysts read on the non-human blastocysts of the instant invention, as required by claim 1.

The mouse blastocysts differ from those used in the instant claims in that the cells of the internal cell mass (ICM) do not have a reduced or restricted survivability compared to corresponding wild-type blastocyst ICM cells. However, it is submitted that selection of blastocysts which do have a restricted or reduced survivability compared to corresponding wild-type cells for use in the method of Geiger et al, would have been obvious to one of ordinary skill in the art at the time the invention was made. Use of blastocysts which have ICMs having a reduced survivability would reduce competition between endogenous stem cells and implanted stem cells for stem cell niches during development. Geiger et al do note that competition between implanted HSCs and endogenous HSCs is a factor in decreased donor cell contribution to cells in the mature animal (See Geiger et al, Pg. 1061, Discussion: The Fate of HSCs Introduced by Blastocyst Injection, first paragraph). Use of blastocysts having a reduced survivability in blastocyst injection methods was known in the art at the time the invention was made, see Eggan et al. Tetraploidy in blastocysts is ultimately lethal to the cells of the ICM, thus donor cells injected into the tetraploid blastocyst are ultimately without competition, and the donor cells will give rise to all cells of the developing embryo (See Eggan et al). Eggan et al disclose means for inducing tetraploidy in blastocysts via electrofusion of two or more zygotes (See Eggan et al, paragraph 0038).

Therefore, use of blastocysts having ICM with reduced survivability reduces the competition between the injected donor cells and the endogenous cells for contribution to developing cell types. Because Geiger et al desired to study the ability of the injected cells' potential to contribute to developing cell types, it would have been obvious to one of ordinary skill in the art to use tetraploid blastocysts, or

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blastocysts which otherwise had ICM with reduced survivability, in order to reduce the competition between the injected donor cells and endogenous cells. One would have had a reasonable expectation of successfully producing blastocysts with tetraploid genetic make up based on the disclosure of Eggan et al. (Claims 1 and 8).

It is further submitted that other methods of genetically altering the survivability of the ICM of the blastocyst, either by introduction of a vector which codes for a gene which reduces survivability of the endogenous ICM cells, through use of antibodies against the native ICM cells, or addition of an antibiotic or additive to which the donor cells are resistant, would also have been well within the purview of one of ordinary skill. Methods of genetic engineering of cells, including blastocysts were well known in the art, and thus the artisan of ordinary skill would have been able to successfully produce a blastocyst and/or donor cell with the desired resistance, or susceptibility to various culture conditions, antibiotics, or antigens, as required to impart the desired reduced survivability to the cells of the ICM of the blastocyst, for the reasons discussed above. (claims 9-12)

Finally, it is noted the murine blastocysts differ from those required by instant claim 16, as they are not pig blastocysts. However, it is submitted that the animal source of the blastocyst would have been a matter of experimental design choice. Both porcine and murine cells were available at the time the invention was made, and thus selection of either animal source would have been within the purview of the artisan of ordinary skill. (claim 16).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651